



Review

Lymphoproliferative disease and cancer among patients with common variable immunodeficiency

S. Gangemi^{a,b,1}, A. Allegra^{c,*}, C. Musolino^{c,1}^a School and Division of Allergy and Clinical Immunology, Department of Clinical and Experimental Medicine, University Hospital "G. Martino", Messina, Italy^b Institute of Clinical Physiology, IFC CNR, Messina Unit, Messina, Italy^c Division of Hematology, Department of General Surgery and Oncology, University of Messina, Messina, Italy

ARTICLE INFO

Article history:

Received 8 November 2014

Received in revised form 1 February 2015

Accepted 2 February 2015

Available online 9 February 2015

Keywords:

Common variable immunodeficiency

Lymphoma

Gastric cancer

Immune dysregulation

Innate immune deficiency

ABSTRACT

Innate immune deficiencies are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. This review discusses the latest insights into the links between common variable immunodeficiency (CVI) and malignancies.

Although Ig therapy greatly reduces the number of infections and enhances survival, it does not appear to address the development of cancer, especially lymphoma. The reasons for the increased susceptibility to lymphoid malignancies are unclear. These include genetics, immune dysregulation, radiosensitivity and chronic infections such as *Helicobacter pylori*, EBV, human herpes virus type 8 and cytomegalovirus.

Further studies will allow us to better stratify the risk for cancer in these patients, and teach us to better prevent these complications and to better treat them.

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1. Introduction

Usually, researchers divide host defense into two harmonizing compartments: innate and adaptive. These work together to efficiently prevent, control, and when necessary destroy the broad range of pathogens that challenge vertebrates. While T- and B-cell-mediated adaptive immunity needs DNA rearrangement and

amplifies its response upon re-exposure to the same antigen, resulting in long-lasting specific immunity, the innate system is preformed in the germline. Innate immunity comprises epithelial and mucosal barriers, natural antimicrobial products, pattern-recognition receptors, and cytokines.

Innate immune deficiencies are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. Although we have an inclination to combine immune deficiencies into subgroups based on cell types or compartments (T cells, B cells, NK cells, complement, phagocytes), these compartments synergistically interact, creating the complex entity known as the immune response [1].

* Corresponding author at: Division of Hematology, Department of General Surgery and Oncology, University of Messina, Messina, Italy. Tel.: +39 0902212364; fax: +39 0902212355.

E-mail address: aallegra@unime.it (A. Allegra).

¹ These authors have equally contributed to the work.

Common variable immunodeficiency (CVI) is a clinically significant immune defect [2,3]. It is a heterogeneous group of disorders, characterized by hypogammaglobulinemia [4], and the incapacity to make specific antibodies in response to immunization [5]. Defects in cellular immunity, which occur in approximately one third of patients, likely contribute to their susceptibility to conventional and opportunistic pathogens.

CVI is the most common symptomatic primary antibody disorder in adults, with monogenic causes identified in less than 10% of all cases. Although there are no clear-cut data on the prevalence of CVI, prevalence ranging from 1:10,000 to 1:50,000 or 1:100,000, is estimated [6–8].

Presentation is variable, both in terms of clinical features and patient age, although patients usually present with recurrent bacterial infections. CVI may also present with characteristic non-infective complications. Based on the complications, distinct clinical phenotypes have been proposed.

In an effort to elucidate the association between all disease-related complications and prognosis, a large European cohort of CVI patients (with an average follow-up of 25.6 years) was studied [2]. Five phenotypes were defined: infections only, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancies. Diverse phenotypes were associated with different survival times: those subjects without disease complications (infections only) surviving longer than those with autoimmunity (relative risk (RR) of mortality, 2.5), enteropathy (RR, 3.0), polyclonal lymphocytic infiltration (RR, 4.0) and, not unexpectedly, lymphoma (RR, 5.5). Polyclonal lymphocytic infiltration (in lung, lymph node, spleen or unexplained granuloma) was associated with a 5-fold increased risk of lymphoid malignancy occurring late in the disease ($P=0.007$). High polyclonal IgM levels were found to correlate with the development of lymphoma in this series [2].

More recently Cunningham-Rudles pointed out that CVI consists of 2 phenotypes, one in which infections are the characteristic and another in which impressive inflammatory and/or hematologic complications also develop, including lymphadenopathy, splenomegaly, autoimmune cytopenias, enteropathy, and/or granulomatous disease. These phenotypes appear to be stable, are related to immunologic and inflammatory markers, and are predictive of outcomes [9].

Although Ig therapy greatly reduces the number of bacterial infections and likely enhances survival, it does not appear to address the characteristic inflammatory complications and the development of cancer, especially lymphoma.

In fact, a higher frequency of malignancy has been reported in these patients [10–16]. The incidence in CVI is around 11–13% and usually occurs during the fifth or sixth decade of life, with a risk 12–18 times higher than the general population [17]. In 2002, a combined study from Denmark and Sweden, using national cancer and immunodeficiency registries, found a increased incidence of 12-fold [13].

The most common sites of involvement are the gastrointestinal tract and the lymphoid tissues.

In fact, there is no doubt about the significantly higher incidence of gastric cancer in patients with CVI [18].

2. CVI and gastric cancer

Helicobacter pylori infection and pernicious anemia are risk predictors for gastric cancer in the general population and probably in patients with CVI. Dhalla et al. performed a review of the literature for gastric cancer and conducted a cohort study of gastric pathology in 116 patients with CVI under long-term follow-up. Regardless of the presence of pernicious anemia or *H. pylori* infection, patients with CVI have an increased risk of gastric cancer and are therefore

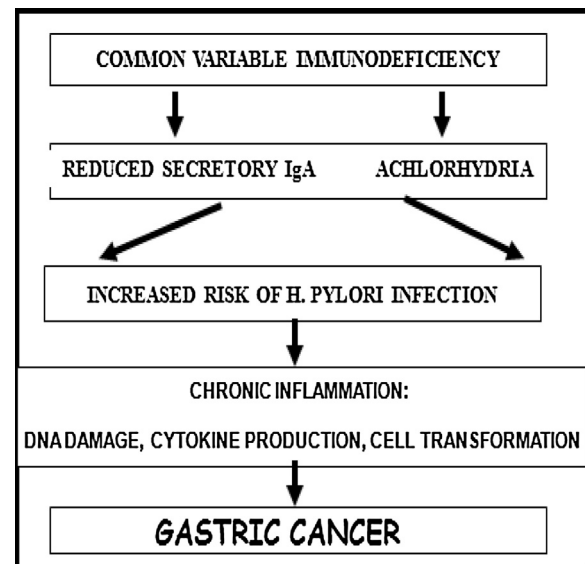


Fig. 1. Mechanisms of gastric cancer in CVI patients.

a high-risk population [19], and there are some reports of gastric cancer presenting at a young age in patients with CVI.

The increased risk of gastric cancer in patients with CVI was recognized in 1985, when a prospective study of 220 patients with CVI followed for 11 years reported a 47-fold increased risk [20]. In a different study, patients with CVI also have a 10-fold increased risk of gastric cancer [13], while in one study, 16% of 120 patients with CVI in the Immunodeficiency Cancer Registry had gastric adenocarcinoma [10]. A multi-center study using Scandinavian cancer and disease registries reported a SIR of 10.3 (95% CI 2.1–30.2), but no increased risk in family members of patients with CVI [13]. This suggests that the increased risk of gastric cancer in CVI relates to the immunodeficiency rather than to genetic traits or *H. pylori* virulence shared with relatives.

Nevertheless, outcome studies of large CVI cohorts followed for medians of 11 and 7 years, respectively, found only four cases of gastric carcinoma in 472 patients [4,12], indicating that the absolute risk is low (about 1% per decade). A different study [21], showed an even lower SIR of 6.1 (95% CI 1.26–17.84). While variability in prevalence from different locations is not surprising, the considerable differences, especially over time, suggest that environmental factors are important [22].

The mechanisms underlying an increased frequency of gastric cancer in CVI are not understood (Fig. 1). Specific antibodies (secretory immunoglobulin IgA) have been shown to kill *H. pylori* in vitro, and the absence of such antibodies in patients with CVI [23] may contribute to the risk.

However *H. pylori* infection does not seem to be more frequent than in the general population, and although there are no formal studies, gastric pathology does appear to be more frequent. In 1999 an Italian group studied gastric pathology in a cohort of 65 patients with CVI after finding that more than 50% had dyspeptic symptoms. Upper gastrointestinal endoscopy revealed that 14 of 34 patients had *H. pylori* infection, 80% of which was associated with chronic atrophic gastritis. In this series, two of 34 had neoplasia (one adenocarcinoma and one high-grade dysplasia), consistent with an increased risk of gastric cancer in CVI [24].

Furthermore, achlorhydria, which compromise defense against *H. pylori* infection in CVI patients, suggests a different cause for gastric cancer.

De Petris et al. determined the morphological features of CVI-associated gastric adenocarcinoma (CAGA) and of the background

gastritis. The population of gastric cancer patients with CVI of Mayo Clinic in the period 2000–2010 was studied; 6 cases of CVI were found in 5793 patients with gastric cancer in the study period. Each patient underwent gastric resection for which histology slides were reviewed. Chronic gastritis variables, CVI-related findings, and features of the adenocarcinoma were recorded. CAGA was of intestinal type, with high number of intratumoral lymphocytes (ITLs). Cancer was diagnosed in younger patients than in the overall population of gastric cancer. Severe atrophic metaplastic pangastritis with extensive dysplasia was present in the background in 4 cases, with features of lymphocytic gastritis in 2 cases.

Gastric adenocarcinoma at young age with ITLs, accompanied by atrophic metaplastic pangastritis, should alert the pathologist of the possibility of CAGA. It follows that, in presence of those characteristics, the search of CVI-associated abnormalities should be undertaken in the nonneoplastic tissues [25].

3. CVI and lymphoproliferative disorders

Several neoplastic diseases have been reported in CVI patients. Rapidly progressive hepatocellular carcinoma in the absence of any preexisting liver disease has been described [26], while, Van den Brand et al. presented a patient with immunodeficiency who died of a metastatic angiosarcoma of the liver [27].

However, although the overall incidence of malignancies in CVI appears to have increased, the data for cancers other than lymphoma are difficult to separate out.

Data on Australian patients notified voluntarily to the Australasian Society of Clinical Immunology and Allergy Registry (1990–2008) were linked with national death and cancer registries. Person-years of follow-up commenced from up to 15 years before registration on the CVI Registry or January 1982, the inception of national cancer registration. Site-specific, 5-year age-, sex-, calendar year-, and state-standardized incidence ratios with 95% confidence intervals (95% CIs) were calculated for all cancers except nonmelanocytic skin cancer. In this study of 416 CVI subjects, there was a 5-fold increase in cancer overall, but lymphoma/leukemia was 31.5% of the total [22].

In the US report, performed on 248 consecutively referred CVI patients of age range 3–79 years who have been followed for a period of 1–25 years, 8.2% of CVI patients had a lymphoid malignancy, all B cell in type. As noted in earlier reports [4,28], lymphoma was more common in females than males (P 0.04). Of these, non-Hodgkin B-cell lymphomas were the most common, with some of these being further classified into specific B-cell phenotypes, including mucosa-associated lymphoid tissue lymphoma, marginal zone lymphoma, and T cell-rich B-cell EBV-associated lymphoma. Monoclonal B lymphocytosis was also noted.

Lymphomas in CVI are usually extranodal, B cell in type, and, unlike lymphomas in other congenital immune defects, are more common in subjects in the fourth to seventh decade of life and are usually EBV negative [28,29]. Cancers of other sorts also developed in 33 patients (7%) in this study. Other large series have not noted this high a percentage of lymphoma: 1.6% in Italy, 3% in the ESID study, 3.8% in a previous United Kingdom study, and 2% in a combined Danish/Swedish cohort [12,13,30]. In Danish/Swedish study Authors examined the risks for cancer among 562 patients with CVI or IgA deficiency and 2071 relatives in 1958–1996. The patients were identified through an Immunodeficiency Register and hospital records, while the relatives were traced through population registers. Cancer incidence was assessed by linkage to the Cancer Registries and compared with that in the general population. Lymphoma, found in 39 cases (8.2%), was the second most common cause of death in a different cohort [29]. For unclear reasons, this is a higher overall incidence than other studies [11–13].

Lymphoma as a complication of CVI is present in female patients with an average of 9 years after diagnosis of CVI; the median age at diagnosis is 23 years [11,20]. CVI patients may present non-Hodgkin's lymphoma generally in 6th and 7th decades and rarely in pediatric population [7].

Hyperplasia is more frequent than malignant disorders, with approximately 50% of CVI patients presenting with lymphadenopathy, splenomegaly and/or gastrointestinal nodular lymphoid hyperplasia.

Petrilli et al. reported a 7-year-old girl affected by CVI who developed multiple Epstein–Barr virus-associated tumors, represented by bilateral adrenal smooth muscle tumors (EBV-SMT) and multifocal diffuse large B-cell lymphoma [31], while Polizzotto et al. reported a case of Burkitt lymphoma in a CVI patient [32].

MALT lymphomas were frequently reported. A recent review of extranodal marginal zone lymphomas in CVI patients reports eight cases of MALT-lymphomas, none of them of gastric location [24,33]. Several other cases of MALT lymphomas, localized in the lung and salivary glands were published [34–36].

As far other lymphoproliferative disorders, Aghamohammadi et al. reported 2 siblings with CVI who developed Hodgkin lymphoma. However, their father and 1 uncle were also affected by the same cancer with no immunodeficiency state [37].

Recent observations indicate that CVI should be added to the list of diseases associated with increased numbers of LGLs [38,39].

Finally, a subset of CVI patients with a distinct T-cell immunophenotype, splenomegaly and granuloma formation has been described. Jesus et al. reported a patient with CVI with T-cell lymphoma mimicking juvenile systemic lupus erythematosus (JSLE). The necropsy showed hepatosplenic T-cell lymphoma with diffuse involvement of bone marrow, spleen, liver, and lungs. The lymphoma cells were positive for CD3 immunostaining and negative for CD20 and lysozyme [40].

Gammon et al. presented 4 cases of CD8(+) Granulomatous cutaneous T-cell lymphoma (G-CTCL). Patients presented with papules and nodules on the trunk and extremities without antecedent patch or plaque disease. In all cases, biopsy specimens revealed a dense granulomatous infiltrate accompanied by an atypical lymphoid infiltrate of CD8(+) T cells. T-cell clonality studies were positive in 3 of 4 cases. Staging was negative for nodal involvement, but lung granulomas were seen in all cases [41].

4. Diagnosis of lymphoma in CVI patients

The lymphomas that arise in patients with immunodeficiency or immune dysregulation differ from those arising in immunocompetent hosts [42].

Lymphadenopathy is very common in CVI and evaluation of these is not simple; when new nodes appear and persist, biopsy may be required. However, lymphomas are more commonly extranodal and appear in unusual locations, and are thus not amenable to standard follow-up measures. Bone marrow examinations to look for lymphoma have not been revealing, with the exception of advanced cases in which the diagnosis was already established by other means.

In addition, the underlying alterations of lymphoid tissues observed in patients with immune disorders have an impact on the usual criteria for the diagnosis of lymphoma. For example, extra-nodal lymphomas arising in MALT, produce prominent lymphoid infiltration of extra-nodal sites that usually lack lymphoid tissue, such as the lung or the stomach. However, patients with CVI often exhibit marked lymphoid infiltration of a reactive nature in MALT-associated sites, making the distinction between benign and malignant lymphoid proliferations ambiguous. Criteria for the diagnosis of malignancy include demonstration of a monoclonal

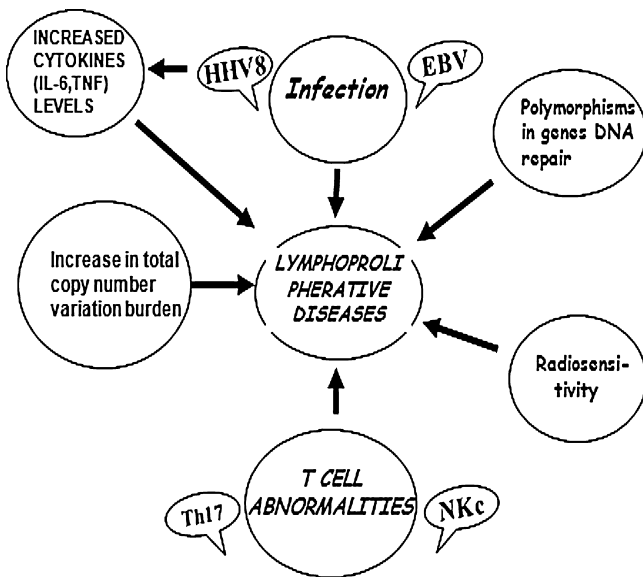


Fig. 2. Pathogenesis of lymphoproliferative diseases in CVI patients.

process either by immunophenotypic or molecular means and in some cases, the acquisition of cytogenetic aberrations.

Higher baseline serum IgM levels were associated with increased risk of lymphoma. In this regard, females with CVI had higher levels of serum IgM, and greater numbers of isotype switched memory B cells, and possibly not coincidentally, a higher incidence of B-cell lymphoma [4,28,29,43].

As far the prognosis, serum levels of sCD30 in the patients with CVI were significantly increased in comparison with controls (36.93 ± 32.38 vs 5.27 ± 1.32 U/ml, $P < 0.001$). The group of patients with splenomegaly and reversed ratio of CD3+CD4+ T cells/CD3+CD8+ T cells had the highest serum levels of sCD30 (66.01 ± 43.34 U/ml) in comparison with other patients ($P = 0.010$). High levels of sCD30 in the CVI patients with splenomegaly and the presence of lymphoma in a patient with the highest level of sCD30 may suggest a soluble form of this marker as a prognostic tool in such diseases [44].

5. Pathogenesis of lymphoproliferative disease in CVI patients

The reasons for the increased susceptibility to lymphoid malignancies are unclear.

Patients who have defective immune responses may be susceptible to malignancies due to complicated underlying mechanisms. There are several reasons for an increased risk of lymphoma in CVI patients, and these include genetics, immune dysregulation, radiosensitivity and chronic infections (Fig. 2).

The interaction between chronic infections and the development of lymphoma is still unclear but studies to clarify this may lead to prevention measures and lymphoma reduction strategies [45]. In fact, the observed prevalence of lymphoma may be due to virus infection or reactivation of weakness of the immune system. Furthermore, CVI patients with systemic and local granulomatosis are more susceptible to developing lymphoma; the diseases may have the same origin, i.e., immune dysregulation and infection with B-cell lymphotropic human herpes virus type 8 (HHV8). HHV8 is a γ -herpes virus that also is known as Kaposi's sarcoma (KS)-associated virus [46]. In the context of secondary immunodeficiencies, such as HIV-1 infection or organ transplantation, HHV8 is an opportunistic pathogen that is linked

to the development of lymphoproliferative diseases (e.g., primary effusion lymphoma and multicentric Castleman's disease). The proclivity of HHV8 to cause lymphoproliferative disorders in the setting of immunodeficiency, together with observations that CVI-GLILD (granulomatous/lymphocytic interstitial lung disease) patients were highly susceptible to lymphoproliferative disease, prompted to determine if HHV8 infection was present in the blood and affected tissues of patients with CVI and GLILD [47]. Moreover, levels of inflammatory cytokines, such as IL-6 and TNF- α , also are elevated in HHV8-induced malignancies [20]. IL-6 enhances the replication of HHV8 and TNF- α and IL-6 may play an important role in the promotion of HHV8-induced malignancies [48].

Therefore, it is possible to hypothesize that the lymphoproliferative disease that is seen in the CVI-GLILD cohort of patients, is due to the unique interplay of HHV8 infection, cellular and humoral immunodeficiency, and polymorphisms within the promoters of inflammatory cytokine genes (Table 1).

It is possible that other viruses, in addition to HHV8, are involved in the pathogenesis of lymphoproliferative disorders in CVI [49,50]. EBV is found in a small number of B cell lymphomas in patients with CVI, including in one patient with an HHV8-negative, primary effusion lymphoma [51]. Prospective studies that examine larger numbers of patients need to be performed to determine the role of these and other transformation-competent viruses in the etiology of lymphomas that occur in the context of CVI.

Importantly, more than half of the CVI patients has T-cell abnormalities including decreased lymphocyte response to mitogens and microbial antigens [52]. This has been proposed as an explanation for the increased risk of malignancy, in keeping with the increased prevalence in other groups with low CD3 numbers such as in HIV infection. However, low numbers of CD3 cells in CVI patients are associated with opportunistic infections and not with lymphoid malignancies, though there are low numbers of such patients in any series [53].

Approximately, half of the cases have signs of T-cell deficiencies contributing to the defective antibody production [4,54]. It's demonstrated that CVI patients have decreased numbers of T-helper-17 (Th17) cells in their circulation [55].

Mutations have been identified in various B-cell related inducible T-cell costimulator (ICOS), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B-cell activating factor-receptor (BAFF-R), in members of the CD19-B-cell receptor (BCR) complex (CD19, CD21 and CD81) and CD20. Moreover, polymorphisms in genes involved in deoxyribonucleic acid (DNA) repair (MSH5, MSH2, MLH1, RAD50 and NBS1) have also been reported in patients with CVI [56–63].

Lower total and CD4+ T cells and natural killer cells in terms of number and function have been strongly associated with risk for subsequent development of malignancy in CVI patients [45].

A reduction in the number of iNKT cells in patients with CVI compared with healthy controls was also observed, and a significant association was seen between the number of iNKT cells and the percentage of class-switched memory B cells and propensity to lymphoproliferation in patients with CVI. iNKT cells are deficient and/or functionally impaired in most of the patients with CVI [64].

However, the relationship between T and B-cell abnormalities remains unclear. A subset of CVI patients harbors a polyclonal expansion of large granular lymphocytes (LGLs) with a distinctive T-cell immunophenotype characterized by CD4/CD8 ratio < 0.9 , in some cases due to an increase in CD8+ T-cells expressing CD57 [65].

The inherent genetic instability of lymphocytes and sustained activation and proliferation of the lymphoid system during infections increases the risk of malignant transformation [66,67]. The finding that genes involved in lymphoproliferation are significantly associated with particular subgroups of CVI patients in the recent genome-wide association, and gene copy number variation study

Table 1

Studies on increased incidence of lymphoproliferative disease and gastric cancer in CVID patients.

	Authors	Year of pub.	CVID patients	Study	Ref.
Lymphoproliferative disease	Hermaszewski et al.	1993	240	Retrospective study	[11]
	Quinti et al.	2007	224	Multicenter prospective study	[12]
	Mellenkeyar et al.	2002	176	Retrospective study	[13]
	Cunningham-Rudles et al.	1987	98	Prospective study	[29]
	Reichenberger et al.	2001	1	Case report	[34]
	Cunningham-Rudles et al. (Am J Hematol)	2002	5	Case report	[35]
Gastric cancer	Cunningham-Rudles et al.	1999	248	Retrospective study	[4]
	Gompels et al.	2003	29	Retrospective study	[10]
	Quinti et al.	2007	224	Multicenter prospective study	[12]
	Mellemkjaer et al.	2002	176	Retrospective study	[13]
	Dhalla et al.	2011	116	Cohort study	[19]
	Kinlen et al.	1985	377	Prospective study	[20]
	Vajdic et al.	2010	1132	Retrospective study	[22]
	Zullo et al.	1999	34	Prospective study	[24]

supports this theory. CVI has been associated recently with a dramatic increase in total copy number variation burden, the cause of which is unclear. However, in order to explore further the origin and clinical relevance of this finding, Keller et al. quantified the total genomic copy number variation (CNV) burden in affected patients and evaluated clinical details in relationship to total CNV burden. Higher total burden did not correlate with incidence of malignancy. These findings could suggest that the increased CNV burden is static and intrinsic to CVI as a disease [68].

In any case, genes were found to be significantly associated with the subsequent development of lymphoma, including PFTK1 that is constitutively expressed at high levels in B cell lymphomas. A significantly high number of patients were found to have duplications in a gene for initiation of DNA replication, namely ORC4L, which is associated with B cell lymphoproliferative disorders. However, such studies are in the beginnings and need to be confirmed before they can be used as predictors of clinical phenotypes in CVI [69,70].

Newly identified disease genes within the CVI population, have advanced the understanding of human immunodeficiency and the molecular basis of B-cell biology [71–78]. Five different G protein-coupled sphingosine-1-phosphate (S1P) receptors (S1P1–S1P5) regulate a variety of physiologic and pathophysiologic processes, including lymphocyte circulation, and cancer. Although B-lymphocyte circulation plays an important role in these processes and is essential for normal immune responses, little is known about S1P receptors in human B cells.

To explore their function and signaling, Sic et al. studied B-cell lines and primary B cells from control subjects, patients with leukemia, patients with S1P receptor inhibitor-treated MS, and patients with primary immunodeficiencies [79]. Showing that different B-cell populations express different combinations of S1P receptors, they found that S1P1 promotes migration, whereas S1P4 modulates and S1P2 inhibits S1P1 signals. Expression of CD69 in activated B lymphocytes and B cells from patients with chronic lymphocytic leukemia inhibited S1P-induced migration. Studying B-cell lines, normal B lymphocytes, and B cells from patients with primary immunodeficiencies, they identified Bruton tyrosine kinase, β -arrestin 2, LPS-responsive beige-like anchor protein, dedicator of cytokinesis 8, and Wiskott–Aldrich syndrome protein as critical signaling components downstream of S1P1. Thus S1P receptor signaling regulates human B-cell circulation and might be a factor contributing to the pathology of chronic lymphocytic leukemia, and primary immunodeficiencies.

As for other genes, two adult siblings, one with CVI, of a consanguineous marriage have been reported that carrying a homozygous 24 bp in-frame deletion in exon 2 of the TNFRSF13C gene [63]. One sibling (the brother) had decreased IgG and IgM levels but normal IgA and the other (the sister), who was clinically normal, had a slightly diminished IgG and IgM levels in her serum. In other

studies, heterozygous sequence variations in the BAFF-R gene (CVID4, MIM#613494) have been reported [80,81]. The significance of these mutations on lymphoproliferative disorders is unclear.

6. Immunodeficiencies and hematopoietic system

Several other types of immunodeficiencies are known. These diseases do not only predispose to infection but also bear increased risk of cancer.

A number of independent groups have begun to define novel immunodeficiencies caused by defects in the caspase recruitment domain family, member 11 (CARD11)-B-cell chronic lymphocytic leukemia/lymphoma 10 (BCL10)-mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1 [CBM]) signalosome complex. The CBM complex forms an essential molecular link between the triggering of cell-surface antigen receptors and nuclear factor κ B activation. Germline mutations affecting the CBM complex are now recognized as the cause of novel combined immunodeficiency phenotypes, which all share abnormal nuclear factor κ B activation and dysregulated B-cell development as defining features [82].

Moreover, inherited defects in Non-homologous-end-joining (NHEJ)-mediated-DNA double strand breaks (DSBs) repair, account for ~15% of human severe combined immunodeficiencies [83]. The ability to repair DSBs is especially important for adult stem cells, which are responsible for tissue replenishment in long-lived multicellular organisms. This is best exemplified in the hematopoietic system, which is maintained by small numbers of hematopoietic stem cells (HSCs) in the bone marrow and which by requirement of their function must maintain their genomic stability at all costs. As such, defects in various forms of DNA repair pathways must have deleterious consequences for these cells. Pluripotent stem cells rely heavily on error prone NHEJ to repair IR and culture induced DSBs, which has the potential to lead to genomic instability and cancer [84–88].

Leukocyte adhesion deficiency type 1 (LAD 1 – CD18 deficiency) is a rare disease characterized by disturbance of phagocyte function associated with less severe cellular and humoral dysfunction.

De Moraes Vasconcelos et al. reported a 20 year-old female presenting a partial CD18 deficiency that developed a megakaryocytic (M7) acute myeloid leukemia. The clinical features of the patient included relapsing oral thrush due to *Candida*, cutaneous infections and upper and lower respiratory tract infections, followed by a locally severe necrotic genital herpetic lesion. The patient's clinical features improved for a period of approximately two years, followed by severe bacterial infections. At that time, the investigation showed a megakaryocytic acute myeloid leukemia, treated without clinical improvement [89].

In a different study, Emir et al. evaluated children with primary immunodeficiency that developed NHL. Two patients had ataxia-telangiectasia, one patient had Bloom's Syndrome, and one patient had Wiskott–Aldrich syndrome. Patients had B- and T-cell lymphoma [90].

Dedicator of cytokinesis 8 (DOCK8) is a member of the DOCK180 superfamily of guanine nucleotide exchange factors, which interact with Rho GTPases. Autosomal recessive DOCK8 deficiency is associated with a novel variant of combined immunodeficiency [91]. Zhang et al. described 11 patients who had a combined immunodeficiency with low numbers of T, B, and natural killer cells, extensive cutaneous viral infections, and susceptibility to cancer. These patients had loss-of-function mutations in the gene DOCK8, which is expressed in lymphocytes [92].

Besides lymphopenia, DOCK8 deficiency has several manifestations including cancers related to cutaneous viral infections. Squamous-cell cancers occurred in three of patients who had extensive human papillomavirus infections, and one patient also had cutaneous T-cell lymphoma–leukemia. Impaired CD8 T cells in DOCK8 deficiency suggests that these cancers may be due to impaired tumor surveillance. It is also possible that DOCK8 has tumor-suppressor functions. Indeed, DOCK8 deletions in primary lung cancers, gastric- and breast-cancer lines, and gliomas suggest a role of DOCK8 in tumor suppression [93,94].

Varan et al., evaluated patients with different immunodeficiency syndromes who had developed malignant solid tumors and examined survival rates and prognosis with respect to type of immunodeficiency disease. Twenty-two patients who were diagnosed with malignant solid tumors and immunodeficiency syndromes between January 1972 and February 2003 were analyzed retrospectively. There were 12 (55%) patients with non-Hodgkin lymphoma, 8 (37%) with Hodgkin disease, 1 (5%) with mucinous adenocarcinoma of the colon, and 1 (5%) with brain stem glioma. Fifteen (68%) patients had ataxia-telangiectasia, 3 (14%) had common variable immunodeficiency disease, 2 (9%) had Bloom syndrome, 1 (5%) had combined immunodeficiency, and 1 (5%) had selective immunoglobulin A deficiency. Out of the 15 patients with ataxia-telangiectasia 9 patients had non-Hodgkin lymphoma, 5 had Hodgkin disease, and 1 had brain stem glioma. One of the patients with Bloom syndrome had Hodgkin disease and 1 had colon carcinoma. The overall survival for the whole group was 24%. Overall survival rates in non-Hodgkin lymphoma, Hodgkin disease, colon carcinoma, and brain stem glioma were 17, 44, 0, and 0% ($P=0.25$), respectively. Overall survival in ataxia-telangiectasia patients was 20%. In this series, most of the patients had ataxia-telangiectasia (68%). The survival rates of the malignant diseases were very poor in immunodeficiency. Overall survival in non-Hodgkin lymphoma patients was relatively worse than Hodgkin disease patients [95].

7. Conclusion

The treatment of CVI involves infusion of replacement doses of immunoglobulin, either intravenously or subcutaneously. However, it is unclear whether adequate replacement of immunoglobulins is sufficient to prevent the increased risk of malignancy seen in this disease [96].

In fact, although the survival of subjects with CVI has improved markedly over time, it does not compare to age-matched subjects of the same sex. For the US study, 58% of female patients with CVI survived more than 4 decades, compared with 80% of age-matched female subjects; 53% of males survived compared with 68% of age-matched male subjects. Due to the heterogeneity of the population followed over this period, the median age at death was 44 years (range, 10–90) for female subjects and 42 years (range, 9–79) for male subjects: not significantly different. The predominant causes

of death included respiratory failure from chronic lung disease, lymphoid or other malignancies, or overwhelming infections [15].

Not all complications appeared to be associated with reduced survival. Patients with gastrointestinal disease (HR=2.78; $P=.0004$), liver disease/hepatitis (HR=2.48; $P=.0003$), lymphoma (HR=2.44; $P=.001$), chronic lung disease leading to functional lung disease (HR=2.06; $P=.001$), or malabsorption (HR=2.06; $P=.022$) had reduced survival in this interval compared with CVI patients without these particular complications. In contrast, patients with any of the autoimmune conditions, cancers other than lymphoma, history of splenectomy, presence of granulomatous disease, or the development of bronchiectasis alone, did not have significantly reduced survival over the 4 decades of study.

One of the questions that have arisen is how to follow CVI subjects over time. Due to the heterogeneity of this disease, there are no set rules aside from therapy, regularly scheduled follow-ups, and periodic monitoring of serum Ig levels.

Management of these patients remains problematic. There is a great need to develop new therapeutic approaches in this group. The use of rituximab in combination with CHOP may provide a promising treatment option for B-cell lymphomas associated with immunodeficiency.

Children with primary immunodeficiency cannot tolerate standard chemotherapy regimens. Shabbat et al. reported two children with diffuse, large B-cell lymphoma; one had ataxia telangiectasia and one had common variable immunodeficiency. Both were given rituximab, one as monotherapy and one in combination with a reduced CHOP regimen. Complete remission was obtained in each patient. Use of rituximab as a first-line monotherapy or in conjunction with reduced chemotherapy should be considered to reduce cytotoxic effects [97].

The field of study on the relationship between immunodeficiency and neoplasms is constantly expanding. Continually are being reported connections with other neoplastic hematologic and or solid, and new possible causal links. For instance, the association between chronic myeloid leukemia (CML) and common variable immunodeficiency is unusual, but there are cases of CVI patients with CML [98].

Moreover, it is possible that the immune impairment in CVI may have a role in the development of breast cancer by increasing susceptibility to infection with the mouse-mammary-tumor-virus-env-gene-like 660 base pair sequence, which has been found in 38% of human breast cancers [99]. Further studies will allow us to better stratify the risk for cancer in these patients, and teach us to better prevent these complications and to better treat them.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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